

REMARKS

The Amendments

Claims 1 and 37 are amended to address the 35 U.S.C. §112 rejections as discussed below. Further, claims 1 and 37 are amended to specify the NK-1 receptor antagonists.

Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

The Restriction/Election Requirements

Withdrawal of the Restriction Requirement is noted. The claims which remain “Withdrawn” are withdrawn only pursuant to an Election of Species requirement. The elected species of the NK-1 receptor antagonist is no longer within the generic claim. Thus, examination should proceed on other species. Applicants note the statement in the Office action mailed August 18, 2008, that upon allowance of a generic claim applicants will be entitled to consideration of claims to additional species within the generic claim in this same application. Thus, the non-elected claims are retained herein.

The Rejections under 35 U.S.C. §112, first paragraph

The rejections of claims 1-10, 20-31, 35 and 37 under 35 U.S.C. §112, first paragraphs, for lack of written description and lack of enablement are respectfully traversed.

It is believed that the rejections are rendered moot, at least in part, by the above amendments. The rejections are based on the “solvate” and “hydrate” terms in the claims. Those terms have been removed from the recitation of the NK-1 receptor antagonists and the

solvate term is removed from the recitation of the anticholinergic compounds. Thus, only the hydrates pertaining to the anticholinergic component remains. Because the anticholinergic of formula 1 is only one specific species and hydrates are well known and routinely made in the art, applicants urge that one of ordinary skill in the art would clearly envisage from the disclosure the claimed hydrates of the recited compounds. Further, it would require only routine experimentation for one of ordinary skill in the art to provide and select suitable hydrates for this compound.

Adequate written description under 35 U.S.C. §112, first paragraph, is not imposed under a strict standard but one applied under reasonableness principles, i.e., the disclosure need only "reasonably convey" to those in the art that the inventors possessed the invention; see, e.g., Fujikawa v. Wattanasin, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996). In the instant case, due to the conventional knowledge in the art regarding hydrates, one of ordinary skill in the art is reasonably conveyed that applicants possessed the invention including any hydrates of the specific compounds of formula 1.

The application clearly recites that "hydrates" of the compound of applicants' formula 1 of the instant claims are included in the scope of the claimed invention; see, e.g., the original claims. The "hydrate" term is recited essentially as in the original claims. In such case, there is a strong presumption that an adequate written description of the claimed invention is present; see, e.g., In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976), and MPEP 2163, part I. A.

It is possible that lack of adequate written description may arise for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention. But this is only the case when the claims require an essential or critical

feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art.

There is no basis on the record here to support the PTO's burden to overcome the strong presumption of written description or a showing by the PTO that the "hydrate" aspect is an essential or critical feature and is not conventional in the art or known to one of ordinary skill in the art. To the contrary, the record as a whole would convey to one of ordinary skill in the art that, whether the compounds are in their hydrate form or not, is not an essential or critical feature of the invention. The essential and critical feature of the invention is the nature of the base compound, not whether it is in hydrate form. Further, the enablement discussion below should make clear that providing hydrates of pharmaceutical compounds is routine to one of ordinary skill in the art.

For these reasons, it is urged that the rejection under 35 U.S.C. §112, first paragraph, for lack of written description, should be withdrawn.

The lack of enablement rejection is made based on the allegation that the specification does not enable one of ordinary skill in the art to make and use the hydrates of the anticholinergic compound as claimed. The rejection is based on an analysis of the Wands factors and applicants address these factors below. However, applicants urge that there are other threshold issues to consider before the Wands factors.

Although the Examiner is certainly aware of this, applicants reiterate that adequate enablement of a claim is not viewed merely by what is in applicants' specification. The knowledge of those of ordinary skill in the art must also be considered; see, e.g., DeGeorge v. Bernier, 768 F.2d 1318, 226 USPQ 758 (Fed. Cir. 1985). See also, Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1534, 3 USPQ2d 1737, 1743 (Fed. Cir. 1987), stating: "a patent need not teach, and preferably omits, what is well known in the art." The position

taken in the Office action is that formation of hydrates requires undue experimentation and is unpredictable. Applicants believe that this conclusion was arrived at because the wrong question is being considered. The conclusion in the Office action appears to be based on the question of whether it is routine or predictable – without conducting any experimentation – to determine whether a specific solvent will form a solvate with a specific compound and what the nature of such solvate would be. The correct question should be: Can one of ordinary skill in the art conduct routine experimentation to provide hydrates of the formula 1 compound which would be useful for carrying out the invention and can one of ordinary skill in the art routinely determine the nature of any such hydrates? Applicants submit that this latter question is the proper one because the law is clear that adequate enablement can be provided from the knowledge available in the art and can be provided from one of ordinary skill in the art conducting routine experimentation. Under this correct standard, there is adequate enablement for one of ordinary skill in the art to make and use hydrates as recited in the instant claims.

One of ordinary skill in the pharmaceutical compounds art is well aware:

- of the definition of hydrates and the chemical formula of any theoretically possible hydrate for a given compound;
- that is conventional to provide hydrates of chemical compounds;
- that only routine experimentation in this field is needed to determine what, if any, hydrates of a given compound can be provided; and
- of the solvent, i.e. water, which is used to provide hydrates of compounds intended for use in pharmaceutical applications.

Thus, determining what hydrates for the specific claimed compound could be practically obtained and whether they are suitable for use in pharmaceutical applications involves only routine experimentation in this field.

As additional proof that determining suitable hydrates would be routine, applicants refer to the *Vippagunta* article cited in the Office action to support the rejection and a further article by *Hilfiker*, filed herewith.

The *Vippagunta* article cited in the Office action does not support that one of ordinary skill in the art could not make and use hydrates of a particular compound. *Vippagunta* may support the notion that one of ordinary skill in the art cannot accurately predict – beforehand – whether a particular compound will form a hydrate or what the nature of the resulting hydrate would be. But, as discussed above, this is not the proper inquiry. The article supports that only routine experimentation by one of ordinary skill in the art is needed to identify, prepare and characterize suitable hydrates of a given compound. For example, *Vippagunta* on page 15, top of first column, states:

It has been established that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. (Emphasis added.)

Likewise, the abstract of *Vippagunta* starts with the statement:

Many drugs exist in the crystalline solid state due to reasons of stability and ease of handling ... Crystalline solids can exist in the form of polymorphs, solvates or hydrates. (Emphasis added.)

Also on page 4, first paragraph, *Vippagunta* states:

Most organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms. ... The common crystalline forms found for a given drug substance are polymorphs and solvates. (Emphasis added.)

Moreover, *Vippagunta* teaches various solvates (including hydrates), structural aspects thereof, examples thereof, including preparation techniques and techniques for the characterization thereof, throughout its disclosure; see, e.g., pages 15-18. *Vippagunta* thus demonstrates that one of ordinary skill in the art in the field of pharmaceuticals would know how to proceed in preparing hydrates and how such hydrates would be identified or characterized, e.g., by polarized light microscopy, etc. See the extensive list of techniques identified on column 2 of page 18 of *Vippagunta*. While some experimentation would be required, such would just be routine to those of ordinary skill in the art. Further, it would be routine in the art to determine whether or not hydrates are possible for any specific compound. While predicting what hydrates could be formed before doing any experimentation may be difficult, the formation of hydrates is common with pharmaceutically active ingredients and methods of providing and characterizing them are well-known and widely applied routinely. In sum, *Vippagunta*, rather than supporting a lack of enablement rejection, supports the opposite, i.e., that determining and providing hydrates of the compounds, as recited in the claims, would be well within the ordinary skill in the art with routine experimentation.

Additionally, applicants cite and provide herewith the *Hilfiker* reference (J.Therm.Anal.Cal., vol. 73 (2003), pp. 429-440). This article reflects the state of the art contemporaneous with the time of applicants' invention. The article recognizes the importance in the pharmaceutical industry of polymorphism and solvates, which includes hydrates. *Hilfiker* states (page 429): "Frequently it is quoted that about half of all small organic molecules can exist as polymorphs or solvates. In our experience this number is closer to 80%." *Hilfiker* (page 430) recognizes that it was known to perform polymorphism screening to "reveal all relevant polymorphic forms" and that a number of methods were

known for characterizing the resulting polymorphs, e.g., “differential scanning calorimetry (DSC), x-ray diffraction (XRD), Raman spectroscopy, etc. *Hilfiker* (pages 430-431) discusses that the process of finding and characterizing the polymorphs, hydrates and solvates, involves a number of steps which were known in the art. But *Hilfiker* points out (page 431) that high-throughput screening techniques were available to perform such steps more quickly with less resources. It also describes (pages 430-431) techniques by which multiple, miniaturized experiments can be simultaneously conducted to determine solvates for a compound.

Thus, one of ordinary skill in the art is well aware that hydrate formation is a very common phenomenon associated with drug substances and that the generation and examination of hydrates can be conducted using highly automated techniques. In view thereof, the allegation that undue experimentation would be needed by one of ordinary skill in the art to provide hydrates of the specific compound of applicants’ formula 1 is refuted on the record. In fact, such experimentation is clearly routine in the pharmaceutical field.

Taking consideration of all of the above points, applicants assess the Wands factors and the comments thereon in the Office action as follows.

The Breadth of the Claims – The breadth of the claims is quite narrow with respect to the hydrate term. The current claims are only directed to hydrates of the specific compound of applicants’ formula 1. The fact that hydrates are included does not make the scope of the claims broad. From all of the above evidence, including that relied on to support the rejection, one can only conclude that there would be limited number of hydrates and one of ordinary skill in the art can routinely determine what they are.

The Nature of the Invention – The invention encompasses hydrates of the specific compound of formula (I) and there is no further description of the specific hydrates in the

disclosure. But such does not support a conclusion that the invention is not enabled. As fully discussed above, since providing hydrates would be routine to one of ordinary skill in the art, describing the specific hydrates is unnecessary for one of ordinary skill in the art to carry out the claimed invention.

The State of the Prior Art and the Level of Unpredictability in the Art – This is discussed in detail above. Applicants also take note of the fact that the claims in a large number of more recently issued patents directed to compounds in the pharmaceutical field include the recitation of solvates and/or hydrates therein without specifically describing preparation of them in the specification. Even a small sampling of recently issued US patents exemplifies this, i.e., U.S. Patent Nos. 7,351,841; 7,321,059; 7,320,995; 7,432,272; 7,345,806; each recite solvates or hydrates of the compounds in their claims. This further evidences the conventional nature in the pharmaceutical art to make and use hydrates of the base compound. Again, applicants urge that, when the correct question is considered, making and using the invention is not unpredictable for one of ordinary skill in the art when using experimentation which is routine in the art. In any event, that there is some unpredictability and that some experimentation may be needed do not negate a finding of adequate enablement. The standard for enablement is not absolute predictability but only reasonable expectation of success; see In re Wright, 999 F.2d 1557, 27 USPQ2d 1510,1512 (Fed.Cir. 1993).

The Level of One of Ordinary Skill in the Art – The Office action admits that the level of skill in the art is high, which further supports enablement. A routinely skilled worker in this art would be more than adequately trained to conduct or direct the routine experimentation needed to prepare the claimed hydrates.

The Amount of Direction Provided and the Existence of Working Examples – The Office action further alleges that the specification provides no direction or guidance on how to make the hydrates encompassed by the invention. However, as shown above, it was routine for one of ordinary skill in the art to make hydrates. As stated above, "a patent need not teach, and preferably omits, what is well known in the art." Spectra-Physics. Further, it is well established that no working examples are required to establish enablement; see, e.g., In re Borkowski, 422 F.2d 904, 164 USPQ 642 (CCPA 1970); and, In re Angstadt, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). Particularly in cases like the present, where the allegedly un-exemplified subject matter is a routinely provided derivative of the compounds for which working examples are provided, the presence or absence of working examples would be of minimal relevance in determining enablement. The Office action admits that the base compounds are enabled and examples for their preparation are provided. These base compounds and their pharmaceutical activity is the main characterizing feature of the invention. From this disclosure, one of ordinary skill in the art in the pharmaceutical arts would immediately consider the use of the hydrates of these base compounds and the application clearly describes that hydrates of these compounds are also included in the invention. One of ordinary skill in the art can then readily conduct routine experiments using conventional methods – and even automated methods – to determine the useful hydrates of these compounds. As a result, applicants fail to see how one of ordinary skill in the art would not be able to practice the invention as claimed. It is not necessary for applicants to exemplify formation of a hydrate to enable such a routine derivative of the exemplified base compounds.

The Quantity of Experimentation Needed – Assessing the compounds for providing hydrates would not require undue experimentation. The *Hilfiker* reference cited above makes

clear that high-throughput automated methods were available for determining hydrates. Further, the requirement for some experimentation – even a large amount – does not equate to **undue** experimentation or lack of enablement. Where the experimentation required is merely routine experimentation to one of ordinary skill in the art, it is not undue experimentation and does not support a case for lack of enablement. See, e.g., Wands, at 8 USPQ2d 1404, stating: “Enablement is not precluded by the necessity for some experimentation However, experimentation needed to practice the invention must not be undue experimentation. The key word is ‘undue,’ not ‘experimentation’.” See also Ex parte Jackson, 217 USPQ 804 (Bd. Pat. App. 1982), stating: “The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.” The conventionality in the art of providing hydrates makes their provision routine, rather than undue, regardless of the amount of experimentation needed.

Considered as a whole, applicants urge that the Wands factors clearly support that the claims are reasonably enabled.

As a further basis for traversal of the rejection, applicants urge that, before even considering the Wands factors, a threshold burden lies with the PTO to provide evidence or objective reasoning substantiating the allegation that the enabling disclosure is not commensurate in scope with the claims to support a rejection under 35 U.S.C. §112, first

paragraph, for lack of enablement. See, e.g., MPEP §2164.04 citing In re Marzocchi et al., 169 USPQ 367 (CCPA 1971), which states:

".. a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein..",

and further,

"..it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." (emphasis original).

In the instant case, the specification's disclosure corresponds in scope with the claims since its general description of making and using the invention applies to the full scope of compound of formula 1, which the disclosure makes clear (see, e.g., page 3, line 9; and original claim 1) includes the hydrates thereof. The PTO fails to provide any allegation that the truth or accuracy of the inventors' disclosure is doubted. Nor has any convincing explanation or evidence to support why the PTO doubts the truth or accuracy of the inventors' disclosure been provided. In the absence of such an explanation or supporting evidence, the PTO's initial burden is not met and a lack of enablement rejection cannot be made. The PTO appears to be improperly shifting the burden upon applicants to provide experimental evidence of making and using the hydrates. But this burden is misplaced in the absence of the PTO meeting its initial burden. Applicants urge for this additional reason, that the rejection for lack of enablement should be withdrawn at least for this reason.

For the above reasons, it is urged that the specification provides an adequate disclosure or how to make and use the claimed invention. Thus, the rejection under 35 U.S.C. §112, first paragraph, for lack of enablement should be withdrawn.

The Rejections under 35 U.S.C. §103

The rejections of claims 1-10, 20-26, 28-31, 35 and 37 under 35 U.S.C. §103, as being obvious over Meissner (U.S. Pub. No. 2002/0115680) in view of Dollinger (WO 02/32865) and Podolsky (US Pub. No. 2003/185838), is respectfully traversed.

Meissner (U.S. Pub. No. 2002/0115680) is the publication of the previously relied on Meissner patent (U.S. Patent No. 6,706,726) and, thus, contains the same disclosure. Meissner discloses compounds of its formula I as anticholinergics, particularly for treating asthma or COPD (chronic obstructive pulmonary disease). Meissner does not provide any suggestion of a composition of such compounds together with an NK₁ receptor antagonist.

The Dollinger reference is not in the English language. Thus, U.S. Patent No. 6,747,044 (indicated by INPADOC to correspond to WO 02/32865) is cited for purposes of an English translation thereof and citations are made to the US patent. Dollinger discloses compounds of the formula (I) (col. 1) as being neurokinin antagonists. Dollinger teaches that the compounds are useful for, among other things, treating COPD.

The claims have been amended above to specify the neurokinin receptor antagonist component used in the claimed compositions. The neurokinin antagonists disclosed by Dollinger are not included in the neurokinin receptor antagonist component used in the claimed compositions. Thus, to the extent the rejection is based on a suggestion to combine the anticholinergic of Meissner with a neurokinin antagonist disclosed by Dollinger, such a combination would not result in or suggest the currently claimed invention.

Podolsky teaches that specific trefoil peptide compounds may be used to treat lesions of the respiratory epithelium. Podolsky discloses that the lesions being treated can result from a wide variety of causes (see, e.g., page 1, paras. 0004 and 0010). Such lesions are not

necessarily connected with COPD but are a symptom which can arise as a consequence of many of a variety of circumstances or diseases, for instance, from such varied sources as surgical intervention or intubation or by inhaling smoke, etc. (see, e.g., page 3, para. 0032, of Podolsky). Podolsky discloses that its specific trefoil peptides may optionally be used in combination with second therapeutic agents. Podolsky discloses a large variety of general second therapeutic agents which could possibly be used, i.e., anti-inflammatory agents, non-steroidal anti-inflammatory agents, antimicrobial agents, antihistamines, cholinergic receptor antagonists, neurokinin receptor antagonists, leukotriene receptor antagonists, decongestants, phosphodiesterase inhibitors and beta-adrenergic antagonists (see, e.g., page 1, para. 0012).

One of ordinary skill in the art is not taught by Podolsky that its trefoil peptides or its second therapeutic agents are effective to treat COPD but merely for treating a symptom which might arise from COPD or from any of a number of other varied sources. Lesions of the respiratory epithelium are only in certain situations connected with COPD, i.e., lesions of the epithelium are not a general symptom in COPD. Further, lesions of the respiratory epithelium can also be caused by many different diseases and circumstances other than COPD. Contrary to the allegation in the Office action (page 11), Podolsky does not “expressly teach the administration of neurokinin receptor antagonists in combination with trefoil peptides in the treatment of COPD.” First, there is no specific disclosure of a combination of a trefoil peptide with a neurokinin receptor antagonist in Podolsky. Second, as discussed above, Podolsky only teaches treating lesions of the respiratory epithelium which can be a symptom of COPD but does not disclose or suggest treating COPD itself.

It is alleged in the Office action (page 13) that treating a disease includes treating its symptoms. Whether this statement is true or not is not relevant to the instant situation because the facts are opposite here. Here, the prior art suggests treatment of the symptom –

not the disease. It should be evident that treatment of a symptom does not necessitate or suggest treating the disease. In fact, the Federal Circuit has addressed this very issue and found that a prior art teaching to use an agent to treat one possible symptom of a disease or condition does not amount to a teaching to use the agent to treat the disease or condition itself. See, e.g., Rapoport v. Dement, 254 F.3d 1053, 59 USPQ2d 1215 (Fed. Cir. 2001), finding that treating a symptom of sleep apnea was not the same invention as treating sleep apnea. The Court rejected Rapoport's argument that a count was unpatentable on the ground that the prior art disclosed administering the compound – not for treatment of sleep apnea itself – but for treatment of anxiety and breathing difficulty, a symptom of apnea, stating: “There is no disclosure in the [prior art reference that the compound] is administered to patients suffering from sleep apnea with the intent to cure the underlying condition.” The facts are directly analogous here and the same reasoning of the Court should apply. A teaching to treat the symptom of lesions of the epithelium is not a teaching to treat the underlying condition of COPD.

Additionally, considering the combined teachings of the prior art as a whole, one of ordinary skill in the art would not have been motivated by the reference teachings or have any other reason to combine one of the second therapeutic agents of Podolsky into the Meissner compositions or methods. Meissner is directed to methods and medicaments for treating COPD, whereas Podolsky is directed to methods and medicaments for treating lesions of the respiratory epithelium. As discussed above, these are different methods. Further, even if treating lesions of the respiratory epithelium were considered to also treat COPD – which is not supported on the record – Podolsky still only suggests that its specific trefoil peptides are useful for treating lesions of the respiratory epithelium. Podolsky does not teach what effect the secondary agents may have or that they would be useful for treating lesions of the

respiratory epithelium. Thus, one of ordinary skill in the art could not have a reasonable expectation that the second therapeutic agents, particularly a specific selected one of them, would be effective without being combined with the trefoil peptides which are the main focus of Podolsky.

Even if, contrary to all of the above reasons, one of ordinary skill in the art did have a reason to combine a second therapeutic agent of Podolsky into the Meissner compositions/methods, the claimed invention would still not be suggested. Podolsky lists “neurokinin receptor antagonists” as only one broad category among a wide variety of possible second therapeutic agents. Given the broad teaching, one of ordinary skill in the art would not have been fairly directed to select this specific category of agent to combine with Meissner, particularly in view of the other distinctions discussed above. Further, Podolsky’s teaching of “neurokinin receptor antagonists” does not point one of ordinary skill in the art to the specifically claimed invention, even if this category was selected. Podolsky does not teach, specifically, NK₁ antagonists (i.e., neurokinin receptor type 1 antagonists). There are at least three known neurokinin receptors types and nothing in the art points one of ordinary skill in the art to specifically select the NK₁ antagonists.

Further, each of Meissner, Dollinger and Podolsky are silent as to the combined effect of an anticholinergic and NK₁ receptor antagonist. There is no suggestion that these compounds would be compatible or that their combination would be reasonably expected to succeed for treating a respiratory disease, particularly COPD, or for any other reason.

Finally, none of the cited references provides any teaching at all regarding the specific NK₁ antagonists now recited in the independent claims. As discussed above, Dollinger is the only reference which relates to NK₁ antagonists. But the compounds of Dollinger are distinct from those recited in the instant claims. None of the references suggest that the compounds

recited for the second components in the claimed compositions are NK1 antagonists or that these specific compounds should be combined with the specific anticholinergic of applicants' formula 1 for the purpose of treating COPD or for any other purpose.

For all of the above reasons, it is urged that the combined teachings of the prior art fail to render the claimed invention obvious to one of ordinary skill in the art and the rejection under 35 U.S.C. §103 should be withdrawn.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

Respectfully submitted,

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